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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/808,699	03/25/2004	Marian Nakada	CEN 5017 USNP	5898

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EXAMINER	
HADDAD, MAHER M	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 11/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/808,699	NAKADA ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-7,9 and 13-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-7,9 and 13-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 9/11/06, is acknowledged.

2. Claims 1, 3-7, 9, 13-18 are pending and under examination in the instant application.

3. In view of the amendment filed on 9/11/06, only the following rejections are remained.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claim 18 stands rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the same reasons set forth in the previous Office Action mailed 7/21/06.

Applicant's arguments, filed 9/11/06, have been fully considered, but have not been found convincing.

Applicant argues that the antibody is readily available commercially from Research Diagnostics, Inc as set forth in the specification at page 18, line 20. Applicant concludes that a deposit of the antibody is not required since it is available to the public commercially in the same manner as any other research reagent.

However, biological materials must be known and readily available to the public (See MPEP 2404.01). Neither concept alone is sufficient. The fact that applicant and other members of the public were able to obtain the materials in question from a given company does not establish upon issuance of a patent on the application that such material would continue to be accessible to the public. The applicant did not make of record any of the facts and circumstances surrounding the access to the biological materials from the company, nor is there sufficient evidence as to the company's policy regarding the material if a patent would be granted.

6. Claims 15 and 18 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating an angiogenesis-dependent disease in a mammal in need thereof comprising administering to the mammal an anti-EMMPRIN antibody in an effective amount to inhibit angiogenesis in said mammal, wherein the angiogenesis-dependent disease is cancer; does not reasonably provide **enablement** for a method for treating metastases in a mammal in need thereof comprising administering to the mammal an "EMMPRIN antagonist" in an amount effective treat metastases in said mammal in

claim 15. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim for the same reasons set forth in the previous Office Action mailed 7/21/06.

Applicant's arguments, filed 9/11/06, have been fully considered, but have not been found convincing.

Applicant has not address the issue regarding the "EMMPRIN antagonist" in claim 15.

7. Claims 15 and 18 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons set forth in the previous Office Action mailed 7/21/06.

Applicant's arguments, filed 9/11/06, have been fully considered, but have not been found convincing.

Applicant has not address the issue in claim 15.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1, 3-4, 7, 13-15 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 02/13763 for the same reasons set forth in the previous Office Action mailed 7/21/06.

Applicant's arguments, filed 9/11/06, have been fully considered, but have not been found convincing.

Applicants disagree that the reference anticipates the claimed invention. Applicant contends that invention is directed to a method of treating an angiogenesis-dependent disease in a mammal in need thereof comprising administering to the mammal an EMMPRIN monoclonal antibody or fragment thereof in an amount effective to inhibit angiogenesis. The reference does not disclose or suggest treating an angiogenesis dependent disease and does not disclose any information concerning angiogenesis or how to determine an angiogenesis inhibiting amount of the antibody. Applicant submits that '763 publication only contains a general reference to treating cancer with an anti-EMMPRIN antibody, but contains absolutely no data to support it. Applicant submits that it is nothing more than speculation based on the fact that, in a prior publication, EMMPRIN expressing tumor cells had been shown to up-regulate the expression of MMPs in fibroblasts co-cultured therewith (See page 57 ofWO'763). Applicant contends that there is absolutely no data showing that inhibiting EMMPRIN can have an effect on tumor angiogenesis; or that anti-

EMMPRIN antibodies or any other anti-EMMPRIN constructs can in fact inhibit tumor growth or metastases. Applicant submits that there is no biological data using EMMPRIN antibodies and no biological data in an angiogenesis or tumor model of any kind. Therefore, the reference is completely lacking in enablement. Applicant further argues that one skilled in the art would recognize it for what it is; mere speculation.

It appears that applicant and the examiner differ on interpretation of both the claimed methods and the prior art. Also, applicant relies upon an asserted and claimed mechanism of action but does not provide objective evidence that the prior art teaching of treating the same cancer patient populations with the same compositions comprising anti-EMMPPRIN mAb to achieve the same therapeutic effect differs from the claimed methods. Further, a reference contains an "enabling disclosure" if the public was in possession of the claimed invention before the date of invention. "such possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his own knowledge to make the claimed in invention." In re Donohue, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985). See MPEP 2121.01.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1, 5-6, 9 and 13-17 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 02/13763 in view of US. Pat. No. 6,406,693 for the same reasons set forth in the previous Office Action mailed 7/21/06.

Applicant's arguments, filed 9/11/06, have been fully considered, but have not been found convincing.

Applicant argues that the `693 patent dose not add anything to the rejection since it is directed to antibodies to antibodies to aminophospholipids and does not teach or suggest anything that would be relevant to anti-EMMPRIN antibodies and their use in inhibiting angiogenesis in a tumor. Further Applicant argues that because the WO'763 patent does not fairly teach or suggest the method of the invention, and the ' 693 patent is not relevant to EMMPRIN antibodies, the combination does not render the claimed invention obvious.

Contrary to Applicant assertions, the `693 patent teaches that certain anti-angiogenic therapies have already been shown to cause tumor regressions and that the antibody LM609 also have angiostatic activity. However, in light of their other properties, they are referred to as anti-vascular therapies or tumor vessel toxins, as they not only inhibit angiogenesis but also initiate the destruction of tumor vessels through mostly undefined mechanisms. Their combination with the present invention is clearly envisioned (col., 78, lines 10-64 in particular). Further, the ` 693 patent teaches that the antibody LM609 against αvβ3 integrin also induces tumor regressions. Integrin αvβ3 antagonists, such as LM609, induce apoptosis of angiogenic endothelial cells leaving the quiescent blood vessels unaffected (see col., 81, lines 8-15 in particular). Finally, the `693 patent teaches the benign tumors, such as angioma (see col., 24, lines 6-7 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the LM609 mab against αvβ3 integrin taught by the `693 patent with the anti-EMMPRIN antibody as taught by the `763 publication in a method for treating an angiogenesis-dependent disease such as tumor growth and metastasis.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the antibody LM609 also have angiostatic activity and LM609 against αvβ3 integrin also induces tumor regressions. Integrin αvβ3 antagonists, such as LM609, induce apoptosis of angiogenic endothelial cells leaving the quiescent blood vessels unaffected as taught by `693 patent. Further, "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. . . [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205USPQ 1069, 1072 (CCPA 1980) (see MPEP 2144.06).

However, based on the totality of the record as detailed above, the evidence of obviousness found in the combined reference teachings with Applicant's argument for nonobviousness. The Examiner concludes that the claimed invention encompassed by instant claims would have been obvious as a matter of law under 35 U.S.C 103(a).

12. Claims 1, 4-7, 13-15 and 18 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Looksmart publication 2001 (IDS ref) in view of Sameshima et al (IDS ref.) for the same reasons set forth in the previous Office Action mailed 7/21/06.

Applicant's arguments, filed 9/11/06, have been fully considered, but have not been found convincing.

Applicant argues that the Looksmart publication does not fairly disclose or suggest the claimed invention. Looksmart merely shows that breast cancer cells transfected with GFP-EMMPRIN produce larger tumors and that EMMPRIN can stimulate production of MMPs 1, 2 and 3. It does not teach that EMMPRIN has a direct role in angiogenesis; does not teach or suggest the use of

an EMMPRIN monoclonal antibody; and does not teach or suggest that the use of EMMPRIN antibodies can inhibit angiogenesis. Further Applicant contends that these reports that cells transfected with EMMPRIN responded by producing more MMPs, are generally limited to in vitro studies, and were at best only indirect evidence suggesting EMMPRIN may be linked to angiogenesis. In many cases, the purity of EMMRIN purified from the cancer cells was not determined. Applicant concludes that it is very likely that other pro-angiogenic factors could have been co-purified with EMMPRIN and were accountable for the stimulation in endothelial cells observed. Applicant submits that unless the investigators could show that the effect of purified EMMPRIN on endothelial cells can be neutralized by anti-EMMPRIN antibodies, their findings were not confirmed. Further, Applicant submits that in the Looksmart publication, antisense eDNA and ribozyme constructs failed to block EMMPRIN expression and were inactive in vitro. So there is no evidence that blocking EMMPRIN would have any effect on angiogenesis. Applicant points that the reference is at best a teaching that EMMPRIN transfected cells produce larger tumors. There is no direct evidence that EMMPRIN has a role in angiogenesis. Applicant further argues that even if the reference could be fairly read to suggest that EMMPRIN stimulates tumor angiogenesis in vivo, which the publication does not, it would still be necessary to show with either antibody or antisense (like applicants did) that inhibiting EMMPRIN suppresses tumor angiogenesis to render the claimed invention unpatentable.

Applicant points to the present application contains direct evidence showing:

a. Inhibiting EMMPRIN expression in tumors with anti-sense construct ("EMMPRIN antagonists") directly suppressed tumor angiogenesis in vivo, quantitatively measured by CD31 staining;

b. That inhibiting EMMPR1N led to suppression of VEGF production, a key angiogenic factor, both in vitro and in vivo. This finding is novel and clearly differentiates applicant's findings from others concerning the relationship between EMM.PR.IN and MMP.

Applicant further argues that the Sameshima et al reference merely shows that EMMPRIN stimulates production of MMP-2 activators, and that anti-EMMPRIN antibodies can inhibit MT2- MMP production. This does not show that EMMPRIN has an angiogenic effect or that EMMPRIN antibodies can inhibit angiogenesis directly or that they have any effect on tumors.

Contrary to applicant assertions Looksmart established a direct evidence that EMMPRIN has a role in angiogenesis and determined that EMMPRIN as an angiogenic factor. Looksmart shows that EMMPRIN stimulates tumor angiogenesis in vivo (transfection and injection experiments show that MDA-MB-436 human breast cancer cells transfected with GFP-EMMPRIN can produce much larger tumors in nude mice than vector-transfected cells). Looksmart suggested inhibiting EMMPRIN with antisense cDNA and ribozyme constructs which were not efficient in blocking EMMPRIN expression and consequently are in active in vivo. However, Sameshima teaches that stimulation of MMP-2, MT1-MMP and MT2-MMP production was inhibited by anti-EMMPRIN monoclonal antibody in a dose-dependent manner. One of ordinary skill in the art at the time the invention was made would have been motivated to substitute the antisense

cDNA or riboszyme constructs therapy for the in vivo use taught by Looksmart article with the anti-EMMPRIN monoclonal antibody taught by Sameshima *et al* because the such antibody inhibited MMPs production which contribute to the angiogenesis. Looksmart suggests the in vivo, including human, treatment implicitly.

13. Claim 3 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Looksmart publication 2001 (IDS ref) in view of Sameshima et al as applied to claims 1, 4-7, 13-15 and 18 above, and further in view of Owens *et al* for the same reasons set forth in the previous Office Action mailed 7/21/06.

Applicant's arguments, filed 9/11/06, have been fully considered, but have not been found convincing.

Applicant argues that because Looksmart and Sameshima do not render the claims obvious, the addition of Owens et al does not add anything to the rejection.

However, based on the totality of the record as detailed above, the evidence of obviousness found in the combined reference teachings with Applicant's argument for nonobviousness. The Examiner concludes that the claimed invention encompassed by instant claims would have been obvious as a matter of law under 35 U.S.C 103(a).

14. Claims 9 and 16-17 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Looksmart publication 2001 (IDS ref) in view of Sameshima et al as applied to claims 1, 4-7, 13-15 and 18 above, and further in view of US. Pat. No. 6,406,693 for the same reasons set forth in the previous Office Action mailed 7/21/06.

Applicant's arguments, filed 9/11/06, have been fully considered, but have not been found convincing.

Applicant argues that because the primary references, Looksmart and Sameshima, do not fairly teach or suggest the claimed method, the addition of the '693 patent for other anti-angiogenic agents, does not cure the deficiency in the rejection.

However, based on the totality of the record as detailed above, the evidence of obviousness found in the combined reference teachings with Applicant's argument for nonobviousness. The Examiner concludes that the claimed invention encompassed by instant claims would have been obvious as a matter of law under 35 U.S.C 103(a).

15. No claim is allowed.

16. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

November 8, 2006

Maher Haddad

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